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## Top Ten Myths of Container Closure Integrity Testing

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Three decades ago, testing a container closure system for integrity meant performing a product sterility test. As recently as ten years ago, container closure integrity testing (CCIT) meant microbial challenge tests, or in more progressive circles, dye ingress tests. Advances in package leak testing technology and shared research studies present a new opportunity to redefine CCIT. The following is intended to dispel some of the more popular CCIT misconceptions.

### **Myth 1: Dye ingress tests such as USP <381> Self Sealing Capacity are valid CCIT methods.**

Compendial or International Standards Organization (ISO) dye ingress tests check the capacity of multi-dose stoppers to reclose upon repeated piercing with an injection needle (1, 2). However, these tests are not validated, reliable or sensitive enough for whole package integrity verification (3). Results are generally variable and subjective. Spectrophotometric dye detection does not eliminate risk of false positive or negative results. Another common dye ingress myth is that test method sensitivity is defined as the quantitative limit of dye detection. Rather, leak test method sensitivity is the demonstrated ability of the test to identify packages with specific defects among a random mix of no-leak and with-leak containers. A detection method able to identify minute traces of dye is useless if the ingress test's challenge conditions fail to draw dye into the package, or if the product itself blocks or clogs leak paths.

### **Myth 2: Microbial challenge tests are required to verify package integrity, and/or to validate the sensitivity of an alternate physicochemical CCIT method.**

To many, validating a physicochemical leak test means performing a microbial challenge test comparison. However, no standard microbial challenge method exists to serve as a basis of such a comparison. Microbial challenge tests are notoriously probabilistic. Instead, leak test instrument performance qualification using appropriate traceable leak test standards is recommended. For example, vacuum decay leak test instrument performance can be verified by introducing an air leak into the test chamber via a NIST airflow meter. Post qualification, proper leak test method validation protocols require successful differentiation of multiple positive and negative control packages randomly tested over multiple days of operation (4). In the same way, regulatory agencies previously expected microbial challenge data as part of a new product application for market approval. But today, successful U.S. regulatory agency market approvals may be supported solely with data from sensitive and appropriately validated non-microbial CCIT methods.

### **Myth 3: Valid CCIT methods must detect package leaks as small as 0.2µm in diameter.**

The ideal leak detection method would identify all leaks from 0.2µm in diameter to large, visible defects in any product-package, rapidly, nondestructively and accurately. Such a method does not yet exist. If it did, the greatest challenge to proving its capability likely would be creating a submicron leak in a test package. Simulating submicron leaks with micro-tubes, etc has its own problems (see **Myth 4**). Laser-drilling technology reportedly can create defects as small as about 2- to 3-µm (nominal diameter) in laminate film, or about 4- to 5-µm in a glass vial. Holes smaller are readily blocked with debris and their sizes are not easily verified. Rarely, if ever, has a product recall occurred due to submicron-sized leaks. Instead, sporadic package defects or production processes trending out of control trigger more grossly leaking product missed by routine inspection. The most useful and practical leak test methods find small realistically viable leaks, but also those larger visible defects that are the source of many product-recall headaches.

### **Myth 4: Positive controls (with-leak packages) made by inserting needles, tubes, or pipettes into a package adequately prove CCIT method capability.**

Inserting a wire, needle, tube or pipette into a parenteral glass vial, a syringe barrel or an elastomeric stopper is a less expensive and simple way to create a defect and may be useful for screening leak test methods. But, in many cases, long channels or wires artificially lodged into the package are no substitute for more realistic defects strategically positioned throughout the container, including at critical seal sites. Recent studies using laser-drilled holes in glass vial walls demonstrated that proteinaceous active substance in liquid product formulations may clog defects making it impossible to use leak test methods that rely on gas or liquid flow through the leak, such as vacuum decay or dye ingress (5). This observation might have been missed if other types of artificial defects had been employed, and especially if solution other than the product itself had been used.

**Myth 5: Helium mass spectrometry is the most useful method for package integrity validation.**

Helium mass spectrometry is a highly sensitive leak detection tool for quantitatively measuring leakage from hermetically sealed packages. Historically, helium tests were used to better understand the probability of microbial ingress through known leak paths (6). However, helium mass spec is only as accurate as the concentration of helium in the test package. Flooding a test package with helium tracer gas requires either puncturing the closed package, then resealing the injection site or flooding the package prior to closure. Both approaches are technique-dependent and are destructive to product-filled packages. Prior to leak testing, helium inside the test package can be quickly lost through a large leak, and a meaninglessly low leak rate may result. So while quite useful, helium mass spectrometry is not the method of choice for all parenteral package testing situations.

**Myth 6: High voltage leak detection (HVLD) is a destructive leak test method.**

Scientists from Hospira reported HVLD exposure caused ozone formation in the headspace of a small volume vial package that lead to active substance oxidation (7). Adequate nitrogen flushing eradicated this effect. Clearly, stability testing product exposed to HVLD is prudent. Still, continued successful utilization of HVLD for many types of pharmaceutical products supports this method's value.

**Myth 7: Residual seal force (RSF) is a package integrity test method.**

Residual seal force tests are an indication of the amount of force an elastomeric closure exerts onto the land seal surface of a vial (8, 9). RSF tests are vital for verifying compression seal quality and consistency. However, RSF does not measure leakage. A package can have an ideal RSF and still have a crack in the glass. On the other hand, a low RSF does point to increased leakage risk at the vial/closure interface.

**Myth 8: A patented leak test method is preferred.**

A patented leak test instrument or technology is not necessarily reliable, robust, or sensitive. In fact, it may not work for a given product-package application at all. Before deciding on a leak testing approach or an instrument manufacturer, test, test and test some more. Leak detection predictions based on mathematical models or limited results using a handful of packages are no basis for a major capital purchase decision. Instead, test packaged product multiple times, multiple days, using randomly introduced no-leak and with-leak packages (both small to large defects). Compare various vendors' instruments using a common challenge-package set. Rent an instrument to allow a window of time for data generation before finalizing a purchase decision. Also, make successful instrument installation and validation a prerequisite for final payment to ensure satisfactory project completion.

**Myth 9: Once a container closure system's integrity has been validated, there is no further need for CCIT.**

A single product-package integrity validation study provides a point-in-time measurement that has little value in product-life-cycle quality assurance. It does not take into account day-to-day operational variations or package component lot-to-lot differences. Also, it provides no guarantee that product routinely manufactured and released for use is integral.

**Myth 10: One leak test method works for all product-package systems.**

Numerous leak testing approaches are useful, but none works for all applications. Package integrity technology has greatly improved in the last ten years, to the point that a toolbox of leak testing methods is essential for various product-package applications. Generally, vacuum decay methods are effective for testing powder-filled packages and non-proteinaceous liquid-filled packages (10). High voltage leak detection works well for many package systems containing liquid formulations (5). And frequency modulated spectroscopy with laser-based gas headspace detection is invaluable for packages requiring vacuum or inert gas headspace (11). These nondestructive, rapid leak test methods are today's primary CCIT tools. Other methods will likely move to the forefront of leak detection as technology advances. But the days of relying solely on microbial challenge and dye ingress tests are long gone.

In conclusion, careful exploration of advertised CCIT developments and candid discussions within the pharmaceutical industry to share findings will ensure a meaningful and practical definition of container closure integrity testing—one that will drive improvements in future product-package system design, assembly and overall quality.

#### **About The Author**

Dana Guazzo is the President and founder of RxPax, LLC, a consulting firm committed to providing guidance to the pharmaceutical industry on primary package development. She has worked in the industry for about 28 years with such firms as the R.W. Johnson Pharmaceutical Research Institute, Schering Plough and the Warner Lambert Company.

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